Case Report

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Journal of Clinical Immunology and Allergy

2020
Vol.6 No.2

Arachidonic acid metabolite (15-keto-PGF2Ã Â±) promotes macrophage polarization from inflammatory M1 to anti-inflammatory M2 phenotype in acute myocardial infarction via regulating glycolytic enzyme PKM2

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Abstract

Macrophages play important roles in resolution of inflammation and cardiac remodeling in acute myocardial infarction due to its phenotypic and functional plasticity. Arachidonic acid metabolites are known to regulate the dynamic changes between inflammatory and resolving macrophages. The aim of the present study was to explore the interactions between arachidonic acid metabolites and cellular proteins. We employed ω-alkynyl arachidonic acid as probe to profile the cellular proteins with the capability to form covalent adducts with arachidonic acid metabolites. Following the treatment of RAW264.7 cells with ω-alkynyl arachidonic acid, the cellular proteins were biotinylated via “click chemistry” alkyne-azido cycloaddition, isolated by streptavidin beads and identified by proteomic approach. As a result, glycolytic enzyme pyruvate kinase M2 (PKM2) was identified as a predominant ω-alkynyl arachidonic acid modified protein. We also identified 15-keto-PGF2α as the specific metabolite for covalent binding to PKM2 by HPLC/MS/MS. We further investigated the effects of 15-keto-PGF2α on macrophage polarization and functions. By monitoring the expression of M1 biomarkers (IL-1β, TNF-α, CXCL10, iNOS, CCL2 and IL-6) and M2 biomarkers (IL-10 and arginase 1), we discovered that 15-keto-PGF2α suppressed macrophage M1 polarization and promoted macrophage M1 polarization in RAW264.7 macrophages and bone marrow-derived macrophages. We also found that 15-keto-PGF2α markedly enhanced the phagocytosis of fluorescently-labeled beads or apoptotic H9c2 cardiac cells. By examining the cardioprotective activities of 15-keto- PGF2α in a mouse model of acute myocardial infarction, we found: 1) 15-keto-PGF2α indeed reduced infarct size on day 3 and day 7; 2) promoted the shift of macrophage M1 polarization to M2 polarization based on the immunostaining of M1 biomarker CD86 and M2 biomarker CD206 in hearts after myocardial infarction; and 3) enhanced macrophage phagocytosis of apoptotic cardiomyocytes as a result from myocardial infarction. By elucidating the underlying mechanisms, we found that 15-keto-PGF2α inhibited PKM2 expression and the formation of PKM2 dimer and suppressed nuclear translocation of PKM2. Collectively, 15-keto-PGF2α may exhibit potential cardioprotective effects by promoting macrophage M2 polarization against acute myocardial infarction in a PKM2- dependent manner.

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Note: This work is partly presented at 8th MOLECULAR IMMUNOLOGY AND IMMUNOGENETICS CONGRESS, March 20-21, 2017 Rome, Italy.